Clark Swentzel, Chairman January 29, 1999
Hazard Identification Assessment Review Committee
Health Effects Division

Re: Malathion - December 22, 1998 HIARC Report on the External Peer Review Process

Comments included here are intended to I) address certain general concerns pertaining to the considerations of the malathion data base, and II) render more specific comments on the December 22, 1998 Hazard Identification Review Committee (HIARC) Report on the Re-Evaluation of Malathion in response to the External Peer Review.

I) General Concerns

1) A principal matter of concern is that of the characterization of the malathion data base under the requirements of the Food Quality Protection Act (FQPA). The December 17, 1997 HIARC report of the November 6, 1997 meeting to consider malathion, claimed that the 10X safety factor imposed under FQPA can be lifted based on the assertions that the malathion data base is complete, having no data gaps, and that infants/children are no more sensitive than adults. These findings were repeatedly stated in the December 17 report. These, of course, are conditions to be satisfied by *reliable* data, that must be met under FQPA in order to justify removal of the 10X safety factor imposed by that Act for the protection of infants and children. Now, following the malathion External Peer Review process, the December 22, 1998 HIARC report, while acknowledging on the front page that the committee as convened on November 6, 1997 addressed the sensitivity of infants and children from exposure to malathion as required by the Food Quality Protection Act of 1996, claims that the HIARC is not responsible for making the decisions with respect to FQPA, referring (or deferring) to the June 15, 1998 decision of the FQPA Safety Factor Committee (p. 7). ***As an aside, I would be curious to know what influence the December 17, 1997 HIARC report had on the June 15 decisions of the FQPA Safety Factor Committee***. Also a curiosity is the fact that though it was well known within OPP/HED that malathion was out for External Peer Review, and many of the questions being posed to the reviewing toxicologists pertained to FQPA matters, why the FQPA Safety Factor Committee could not hold in abeyance its assessment until receipt of the External Peer Review. The external reviews were received by HED's External Peer Review Coordinator early in June 1998, who in turn forwarded them to me on June 11. If the HIARC's decisions with respect to FQPA were appropriately rendered November 6, 1997, i.e. prior to the involvement of the FQPA Safety Factor Committee, then the deliberations of the external peer reviewers and all of my comments subsequent to that meeting rightfully should be addressed by HIARC with respect to those November 6, 1997 decisions. On the other hand, if the deliberations of the FQPA Safety Factor Committee should intervene and overide the HIARC decisions of November 6, 1997, then the former committee should have addressed the External Peer Review and my many comments, *to the extent these pertain to FQPA matters*. If the HIARC is now discounting its considerable input into this FQPA consideration as documented in the December 17, 1997 report, then HIARC

is duty bound to refer all matters pertaining to that issue back to the FQPA Safety Factor Committee for appropriate revisions. Proper consideration of the External Peer Review demands nothing less, irrespective of which committee assumes the burden. ***The responsibility of responding to the External Peer Review, FQPA aspects, must be rendered from either one or both of these committees***. Yet there has been nothing of recent vintage forthcoming from the FQPA Committee to suggest its awarness of the External Peer Review, or the facts that the malathion data base is *not* complete and that data gaps *do* exist. The fact of the matter is that data gaps remain at this time and the external peer reviewing expert toxicologists concluded for various reasons and in varying contexts the absence of ***reliable*** data required under FQPA with respect to the sensitivity of infants and children to justify discounting the 10X safety factor. ***This remains a premier matter of concern at this juncture for HIARC, but the short of it is that deletion of the FQPA 10X Safety Factor cannot be defended in light of the conclusions of the External Peer Review of malathion.***

2) The HIARC has set the Chronic RfD at 0.04 mg/kg/day derived from the recent chronic toxicity/carcinogenicity study in the rat. This decision was rendered though two members of the External Peer Review affirmed retention of the human study (RfD = 0.023 mg/kg/day) and the third toxicologist, though supporting the rat study, advocated an additional 3-fold uncertainty factor to address deficiencies (RfD = 0.013 mg/kg/day). So the HIARC has disregarded the recommendations of all the external reviewing toxicologists, as well as my recommendation. In my view, the human study should be retained, with imposition of an added uncertainty factor to address the fact that only males (men) were evaluated in the critical study, *until such time as definitive cholinesterase data in animal models has been obtained.*

3) The HIARC has set the Acute RfD at 0.50 mg/kg/day despite the fact that all members of the External Peer Review say it is not supportable, principally due to the absence cholinesterase activity assessments in the critical study (developmental toxicity study), where body weight change, a relatively insensitive parameter, serves as the basis of the end point. The HIARC decision *assumes* in the absence of actual data that cholinesterase inhibition, or other more sensitive parameters, e.g. behavioral effects, would not be affected after a single dose of this magnitude. Particularly troubling with this decision is the assumption that a single oral dose as high as 50 mg/kg would not elicit cholinesterase inhibition, even though cholinesterase was inhibited after only two weeks exposure in a range-finding inhalation study.

OPP should be setting important endpoints such as the acute and chronic RfDs, at the right levels for the right reasons. This requirement has not been satisfied on either of these endpoints.

4) The HIARC has been advised of the flawed DER for the malathion 2-generation reproduction study. See letters (Attachments) of B. Dementi dated February 10, August 3 and 10 and November 5, 1998. In spite of this claim, there have been no revisions to the DER. ***Since this study is critical to the question of relative sensitivities of young and developing individuals versus adults in deciding whether to retain the FQPA 10X safety factor, it is essential this***

study (or at least the aspects of the study pertaining to the relative sensitivities issue) be re-reviewed by someone external to HED. I recommend either an External Peer Review of the DER and the MRID submission (note: the current External Peer Review toxicologists were not aware of the disparity between the conclusions of the study author and those expressed in the DER), or a denovo review of the submission. In either case, the reviewer(s) should be advised to examine critically the question of relative sensitivities. When the existing DER was prepared, FQPA was not in place and the reviewer was not particularly attuned to the importance of the distinction.

5) When addressing the question of relative sensitivities of young/developing versus adult animals, I noted at the August meetings that two studies on the one-liners showed the young animals to be more sensitive than adults. These studies were: a) a Guideline 81-1 American Cyanamid Company acute oral study on 95% a.i. malathion in the cow, where reportedly the LD50s were 80 mg/kg (calf) and 560 mg/kg (cow); b) an acute intraperitoneal study in male rats on malathion technical [purity not stated, however in reference to the same published work for this study, Substitue Chemical Program 1975 (Malathion) (p. 66) indicates purity as 99%], where the LD50s were 750 mg/kg (adult) versus 340 mg/kg (weanling). There is no acknowledgement of this in the minutes. Also, the Substitute Chemical Program 1975 (Malathion) says: "Young animals appear to be more susceptible to malathion than older animals (Brodeur and DuBoise, 1963)." (p. 67) Along these same lines, I would mention the following publication: Mendoza, C. E. (1976) Toxicity and Effects of Malathion on Esterases of Suckling Albino Rats., Toxicol. Appl. Pharmacol. 35, 229-238. This particular publication has not, to my knowledge, received a formal review. However, it appears in a recognized peer reviewed journal. Among other conclusions reached in this work, the study claims that one-day-old Wistar rats were found to be *nine times* (close, I might add, to that magical 10X factor imposed by Congress) more susceptible to malathion than seventeen-day-old pups. Accordingly, the LD50 for one-day-old rats as performed repeatedly was 209 (ranging 177-250) mg/kg as compared to LD50 values for seventeen-day-old rats of 1806 (ranging 1415-2003) mg/kg. The test material was identified as American Cyanamid 99.3% a.i. malathion. ***Such information as this serves to support the evidence of enhanced sensitivity of young rats evident in the Guideline reproduction study and in turn support the 10X safety factor imposed under FQPA.***

6) An issue not addressed by the HIARC at its August meeting was that of the response of the external reviewers to the question of the adequacy of the malathion data base. This question was posed among a set of preliminary questions to the external reviewers by HED's external peer review coordinator, Dr. Henry Spencer, and I recommended in an August 17, 1998 memorandum (Attachment 16) to the committee chairman that it be discussed. In essence, the external reviewers identify several data gaps or data deficiencies which are summarized in this August 17 letter. Now whether these deficiencies are data gaps in the strict sense of being unsatisfied end points in Guideline studies (as I believe some are), or inadequacies in the overall assessment of malathion to address health effects concerns, is probably one more of semantics than substance with respect to the intent of Congress to protect infants and children. A most notable statement along these lines was made by Dr. Dourson, who wrote: ***"I am not satisfied that the potential***

risk to humans is addressed with the data available in this review package." *(P. 3 of his June 3, 1998 comments).* ***So the point being made here is that it cannot be claimed by HIARC that the no-data-gap qualifier required under FQPA for removal of the 10X safety factor has been met, and thus there is encumbency upon the HIARC to clearly explain the status of the adequacy of the data base after realistically considering the comments of the external reviewers and myself, and whether strict Guideline requirements have been met.***

II) Specific Comments (In my view, the statements made throughout this December 22, 1998 HIARC report under Panel's Response do not adequately portray the contributions made by the external toxicologists, and to that extent serve to devalue the External Peer Review process. Their comments are creative and complex, and I recommend as a preferred evaluation the "Consolidation of External Peer Reviewer's Comments on Malathion non-Cancer Issues", dated July 21, 1998, located under Attachment 12 of the HIARC report.)

P. 2: Though Karl Baetcke was not present at the August 18, 20 or 27, 1998 meetings, he was present and rendered input at the meeting of November 5, 1998. Furthermore, since important matters were discussed on November 5, this date should be included with the above three dates as together constituting the most recent HIARC meeting for the re-evaluation of malathion.

P. 3, paragraph 4: The report should acknowledge the contributions of Dr. Henry Spencer, OPP's External Peer Review Coordinator, in providing preliminary questions to the panel concerning both the acceptability of studies provided the panel and the completeness of the data base.

P. 5, paragraph 6: Statement neglects to acknowledge the Panel's response to question 3) c). The question was: *Is the data available in the developmental toxicity studies sufficiently reliable to discount the 10X safety factor required under FQPA?* This is a key question to which the Panel responded in the negative, *unanimously*. As I understand the purpose of this second series of meetings of the HIARC in August 1998, it was to respond to the External Peer Review process in re-evaluating the malathion data base. If the responsibility no longer resides with the HIARC as it did in November 1997 to address the FQPA 10X safety factor, rather than ignore this question, the HIARC report should acknowledge here the External Peer Review response, while affirming its referral to the proper committee for re-evaluation. ***Either HIARC or the FQPA Safety Factor Committee is responsible for responding to the External Peer Review on this all important question.***

PP. 6-7: The entire discussion under HIARC's conclusion with respect to the 2-generation reproduction study is incorrect. As stated elsewhere, the DER is flawed, principally in not taking into consideration in its conclusions the rather extensive amount of body weight *gain* data presented in the MRID submission, and the citing of that data by the study author in concluding the lack of an effect in parental animals, at any dose. The DER neither acknowledges the body weight *gain* data nor does it attempt to address the study author's views. I have read the study author's conclusions and examined the data he cites in support of his conclusions, and find no disagreement. This has been suitably brought to the attention of the HIARC many months past at

meetings and in the form of memoranda submitted by me which constitute part of this package, yet in spite of that we have arrived at this point with no revisions to the DER, nor any additional written assessment of the MRID submission designed to address the relative sensitivity question that has been identified. Again, the study report itself indicates no effect in parental animals. Yet, offspring were affected at the top two doses, and possibly at the lowest dose, indicating *enhanced* sensitivity of the developing individual. All of your arguments to the contrary presented in this section, absent the actual written evidence to support your conclusion, should be considered unacceptable. In seeking to discount effects in offspring during lactation days 7, 14 and 21 at the penultimate dose level on the grounds that malathion is in the milk in the absence of any evidence showing its presence in the milk, or how much is there, and in the face of the fact that HED's residue chemist says it is absent in the milk of the goat, the surrogate animal used by EPA to set milk tolerances, is simply unacceptable. Similarly, though perhaps not quite so remarkable a departure from reason in discounting offspring effects at the penultimate dose level during lactation days 14 and 21, is the argument that since pups eat more on a body weight basis, their dosing in effect was higher than that of dams at a given concentration of malathion in the food. The problems with this are that it would be less efficacious as an explanation at 14 days (up to which point, as I understand, milk consumption remains predominate as the food source) than at 21 days, and lacking actual food consumption data in a given study, one cannot make supportable, nor indeed *reliable,* conclusions as to how much solid food pups may consume, particularly under the influence of an organophosphate in the diet. The point is, offspring were adversely affected in this study at the penultimate dose level, on a rather crude basis of assessment, body weight changes. There is no cholinesterase data. Arguments employed by the HIARC to discount differences between adult and developing animals do not rise to the level of the ***reliable*** as required under FQPA.

P. 7, paragraph 4: Once again, HIARC disowns its decisions on FQPA issues made in November 1997, and refers to the FQPA Safety Factor Committee decisions of June 15, 1998. You say the committee removed the FQPA 10X safety factor for the reasons provided, i.e. 1) completeness of the toxicology data base (yet as has been explained, the data base is incomplete in many ways); 2) lack of increased susceptibility in developmental and reproductive toxicity studies (yet these topics are among those being taken up by the External Peer Review process, and those external scientists do not agree the said studies provide *reliable* data of the sort required); 3) adequate exposure data. It would seem the FQPA Safety Factor Committee rendered its judgement in the absence of important information presented to HIARC, and its decisions will need to be revised accordingly. I should also note there has been no mention in the HIARC report of those acute studies on malathion showing enhanced sensitivity of young/developing versus adult animals that were presented in my November 5, 1998 memorandum to Clark Swentzel, HIARC Chairman. Such evidence adds to the burden inherent in discounting the 10X safety factor under FQPA that HIARC should acknowledge. ***HIARC should not accept so uncritically the conclusions of the FQPA Safety Factor Committee, knowing that committee may have acted on incorrect or incomplete information.***

P. 7, paragraph 5: With regard to Question 2, the HIARC Conclusion does not address the

question. While it may be true a weight-of-the-evidence approach embraces a number of studies, each study makes its own contribution, and must be evaluated on its merits. Thus, to the extent the reproduction study is important, in this case it does not offer *reliable* evidence of no increased sensitivities between young and mature animals. Where else in the weight-of-the-evidence does one obtain information on relative sensitivities between young/developing and adult animals? The answer to this question is in the developmental toxicity studies, and acute studies that have been cited. However, as explained these studies also do not provide *reliable* data showing no incresed sensitivity among young/developing individuals. The other studies you cite in the weight-of-the evidence do not address the relative sensitivity question. One cannot wave the magic wand of "weight-of-the-evidence" to substantiate that which does not exist. It was a consensus of the External Peer Review toxicologists that additional behavioral effects testing is indicated, and that cholinesterase data not obtained in developmental toxicity and reproduction studies is a deficiency in the data base. ***In view of these outcomes of the External Peer Review, the developmental neurotoxicity study on malathion is indicated as the remedy, i.e. a study to be required.*** It was in part because the HIARC, in previous deliberations, had determined the developmental neurotoxicity study would not be required, that the data base was presented before the External Peer Reviewers for evaluation. You employ circular reasoning when you merely cite the former conclusion, rather than provide a defense as to why, in light of the External Peer Review process, the developmental neurotoxicity study should not be required.

P. 8, paragraph 4: In HIARC's Conclusion concerning Question 3, once again circular reasoning is used in the face of the External Peer Review response. It is because HIARC previously determined the reproduction study provided adequate and reliable data to address the mandates of FQPA that the issue was submitted to the External Peer Review. The external toxicologists have concluded the data are not reliable to address FQPA concerns. Hence, rather than cite HIARC's prior decision, you need to justify ignoring the external reviewers if HIARC is to sustain its decision to remove the 10X safety factor. As before, I question whether exposure assessment data used by the FQPA Safety Factor Committee can be cited in support of removing the FQPA 10X Safety Factor, if the question of relative sensitivity is not satisfactorily rendered in the toxicology data base.

P. 9, paragraph 3: In presenting the Panel's Response to the six questions pertaining to the establishment of the Chronic RfD, the comments are too abbreviated and therefore neglect to provide HIARC's assessment of the questions and answeres provided by the External Peer Review members. The external toxicologists had much to say, the content of which may be found in their appended responses and is summarized in the July 21, 1998 memorandum of B. Dementi. See Attachment 12.

P. 9, paragraph 4: The ***"critical effect"*** found in this quotation from *Dr. Dourson*, one of the external toxicologists, should be identified here in the HIARC report as cholinesterase inhibition. It is important the HIARC make its audience aware of the identity of the effect (cholinesterase inhibition) because it is the basis of the RfD, and that Dr. Dourson considers it a data gap in the two-generation reproduction study. Also, since you have quoted Dr. Dourson, a balanced

approach would necessitate quoting the other external reviewers. *Dr. Hartung*: ***"No. The human is the correct species of concern. Substituting a rodent introduces many more uncertainties than those produced by minor deficits in the analysis of chemical purity or concern about statistical precision."*** (P.7 of his 6/3/98 comments); and ***"Look at what you are doing! Here you are willing to accept a study for which you are also willing to mess around with another factor of 10X, just because the statistical data are neater. In the process you are willing to discount human data, even though it is extremely unlikely that the equivalent statistical uncertainties for the human will reach anywhere close to 10X."*** (P.8 of his 6/3/98 comments). Note he addresses the purity question, and I advised the committee that the human study in question, Moeller and Rider, while not stating the purity, did claim it to be American Cyanamid malathion, the purity of which was known in the industry at the time. Furthermore, at the committee meeting there was an extensive discussion of the fact that the rat may be a poor surrogate for man, based upon differences in carboxylesterase profile in rat versus man. The committee even concluded on August 18 to impose the additional 3-fold uncertainty factor, which yielded an RfD of 0.013 as opposed to 0.04 mg/kg/day. However, the committee reversed itself on August 20, ostensibly because the issue (role of carboxylesterase) may relate to a few other pesticides where it has not been addressed. *Dr. Decker:* ***"Additional testing should be required in the male and female rat before any thought is given to replacing the human data relied on to establish a RfD."*** (p. 5 of his 6/11/98 comments)

P. 9, paragraph 6: Item (iv) claims the animal toxicology data base is complete excepting a subchronic oral study in dogs and a subchronic inhalation study in rats. This is not an adequate rendering of data gaps. The reader is referred to the comments of the External Peer Review members and the supporting background materials provided the external reviewers. ***Indeed, the question of the adequacy of the malathion data base more than any other issue prompted the External Peer Review.*** Also, waiting in the wings are the cancer related issues to be addressed and the attendant data gaps being filled at this time. So, as of this writing, other data gaps remain. Your report should not be preemptive.

P. 9, paragraph 7: Under item (i), HIARC claims a NOEL (not a LOEL) was used to derive the RfD. A close examination of the chronic toxicity/carcinogenicity in the rat from which the RfD was obtained will show that at the end of the first three months (90 days) of testing, there was no NOEL for erythrocyte cholinesterase inhibition among females. Under item (ii), HIARC claims this NOEL is supported by the same NOEL in the subchronic neurotoxicity study in the rat (DER # 10). The problem with this comparison is that while the NOEL in the subchronic study was set at 4 mg/kg/day, there were but 5 rats/sex/group assayed for cholinesterase inhibition, the data were highly variable such that numerical inhibitions of the enzyme were seen at 4 mg/kg/day, though not achieving statistical significance and the doses above 4 mg/kg/day, 395 and 1575 mg/kg/day, do not provide much dose response data for effects at the low dose in question. Rather than the subchronic neurotoxicity study's serving to support the cholinesterase findings in the chronic toxicity/carcinogenicity study, it underscores the need for definitive assessments of cholinesterase inhibition in the rat. In other words, not much reliance should be placed in the subchronic neurotoxicity study in support of a NOEL for cholinesterase inhibition. Under (iii),

the fact that the RfDs calculated from rat and human studies come close to one another may be fortuitous, especially when one considers a 100-fold factor is used for the rat and only a 10-fold factor is used for the human data, and should not be cited as justification to select the RfD based on the rat data. In consideration of the fact that the RfD chosen by the committee is now larger than the former RfD based on the human study, one should think long about switching to the rat data, prior to obtaining more definitive rat data, or seeking to understand the nature of differences in sensitivity between rat and man. Indeed, if the two RfDs are considered comfortably close, why not retain the RfD based on human data? Of course, the answer to this question may be that in sticking with the human data an addeed uncertainty factor, heretofore not employed (perhaps 3 per *Dr. Dourson*), is needed because *women* were not evaluated, while evidence exists in the malathion data base indicating females to be more sensitive. On the other hand, to avoid this dilemma, switching to the rat data should be considered more advisedly than was done at the HIARC meetings. ***The bottom line is that the cholinesterase data base remains inadequate for establishing the proper chronic RfD, which for the moment should continue to be based on the human data.***

P. 10, paragraph 2: In the October 27, 1998 draft report of this meeting, the Panel's Response was worded (p.10) exactly as it is worded here, even though my November 5, 1998 comments attempted to explain the discrepancy. Reproduced here are the actual words from my November 5, 1998 memorandum: **[**P. 9, paragraph 3: The Panel's Response as described is incorrect in light of the following: 1) *Dr. Dourson* advocated 10X as opposed to 3X. 2) *Dr. Decker*, in his follow-up response of 7/21/98 says: ***"Based on my experience (43 years in the field of toxicology), Reference N (TES Process), and the letter from Dr. Dementi (July 9, 1998), I doubt that the 1/3 LOEL is adequate to account for the absence of a NOEL. At the present time it would seem prudent to use 1/10 LOEL." I assume, of course, that further testing will be forthcoming to determine a NOEL, at which time this safety factor should be reexamined."*** 3) *Dr. Hartung* says: ***"This fine-tuning is unwarranted because of major species differences in exposure scenarios."*** This should be interpreted to mean that fine-tuning, 3X or 10X, in his view cannot address the inadequacies. It cannot be taken to mean he opposes increasing the factor from 3X to 10X. Indeed, given his expressed views, proper testing is indicated, but lacking that and until proper data is in place, the implications of his words *convey to me* that he would consider 10X as preferred for public health protection, although he does not actually say that. The bottom line is that two reviewers, a consensus, support the imposition of a 10X safety factor, while the views of the third should be suitably qualified in your report and cannot be simply cited as "one member recommended against the use of an additional UF", left to be interpreted to mean Dr. Hartung sees no need to increase the uncertainty factor because the study is adequate as it stands. Again, *transparency* of your presentation is the issue here regarding Dr. Hartung's comments.**]**

P. 11, paragraph 6: Obviously, the study makes no distinction between susceptibility of young and old animals. However, I am often troubled by statements such as that on your p. 7, paragraph 7, where it is said: "At present the determination of susceptibility is made not based on the results of one study (where in fact one *appropriate* study that is positive will do) but rather on a *weight-*

of-evidence (emphasis added) basis that includes acute and subchronic neurotoxicity studies, the prenatal developmental toxicity studies in rats and rabbits, the 2-generation reproduction toxicity study in rats as well as *the toxicity profile of the chemical* (emphasis added). I put this question forward to make it *transparent* to observers that this major study (combined chronic toxicity/carcinogenicity) does not contribute anything magical to the claim of the weight-of-evidence toward justifying removal of the 10X safety factor for the protection of infants and children. In my view illegitimate mileage is often reaped under the claim "weight-of-evidence" when in fact the well may be rather dry. ***Where the FQPA 10X factor is concerned, if young and developing individuals are shown to be more sensitive compared to adults in either or both developmental or reproduction studies, the factor remains.***

P. 12, Acute Neurotoxicity Study - Retinal Histopathology: Your report should note in citing the results of the November 13, 1997 *ad hoc* group meeting, that referral of the issue to the External Peer Review was born in part out of my disagreement with the *ad hoc* group decision, i.e. that decision was referred to the external toxicologists experts for an opinion. The External Peer Review members were provided the *ad hoc* report along with the complete set of DERs for consideration. Their decision was unanimous that the slides bearing retinal rosette should be submitted for independent confirmation as to diagnosis, and the lower dose group (s) in the study should be examined histopathologically. ***Since receiving the External Peer Review results, the HIARC has offered no new reasons to rebuff the external toxicologists recommendations.*** It is essential a few comments be made at this point in reference to the *ad hoc* report findings as rendered here in the HIARC report. Though but one male rat in the high dose group exhibited the bilateral retinal lesion, there were but *five* male rats so evaluated in that group. FIFRA Guidelines require examination of lower dose group (s) where there has been a finding in the high dose group. Indeed, dispensation from the requirement to examine all lower dose groups is contingent upon negative findings in the high dose group. The term retinal rosette does not convey anatomic description of the lesion. There are recent concerns as to the potential effects of organophosphates on the visual system, a subject not familiar to many pathologists.

P. 13, paragraph 4: Again, the Panel's Response rendered here is inadequate to convey the opinions of the external toxicologists. The reader is referred to the corresponding section under "VI Subchronic Neurotoxicity Study" in the July 21, 1998 Consolidation of External Peer Reviewer's Comments on Malathion Non-Cancer Issues, appearing under Attachment 12 of this HIARC report. ***The bottom line is that at least arguably a consensus exists among the external toxicologists that additional behavioral effects testing, e.g. developmental neurotoxicity, should be required for malathion.***

P. 14, paragraph 5: The HIARC concluded ***".....the entire data base should be examined to see if any peculiarities exist that could serve as a basis for claims of sex-linked sensitivity."*** I agree with this conclusion and trust there will be follow-up.

P. 14, paragraph 6: In saying that there is no consistent difference in sensitivity of males versus females, you neglect to cite your November 13 *ad hoc* committee report which concluded females

were more sensitive. ***The fundamental question that needs to be addressed is whether women (girls) are more sensitive than men (boys), and if so adjust regulatory end points accordingly.***

P. 15, paragraph 4: Panel's Response should say in the case of the one member who said no, qualified his no to be applicable as long as the rat study as opposed to the human study serves as the basis for the RfD. Of course, the question of the appropriateness in using the rat study for the RfD is being challenged elsewhere in this External Peer Review process.

P. 15, paragraph 5: Under section (iii) of HIARC's Conclusion, it is encouraging you have added the phrase "(some studies show fairly large differences)"

III CONCLUSIONS

For the most part, the HIARC has used the same reasoning employed in November 1997 to refute the conclusions/recommendations of the External Peer Review. There is little evidence the HIARC has been influenced by the external toxicologists, whose task it was to weigh in on the differences of opinion between myself and the committee. ***It is not altogether clear to me why the issues were referred back to the HIARC, but in any case, all of the committee's decisions require review and confirmation outside HED (e.g. SAP) before they become regulatory acceptable.*** The following particularly important conclusions are supported by *at least* a consensus of the external reviewers who had the full package of data in hand:

a) An acute (one-day) RfD end point as high as 0.50 mg/kg is not supported by the data base. It is particularly important this be addressed if the acute (one-day) end point finds use in risk assessments for exposures exceeding one day.

b) In the absence of assessments of cholinesterase inhibition in young/developing animals versus older animals in developmental and reproduction studies, and the absence of behavioral effects testing in reproduction studies, it cannot be interpreted that such studies provide the *reliable* information (as required by Congress) of no increased sensitivity of young animals necessary to discount the 10X safety factor imposed under FQPA for the protection of infants and children. To the extent these studies do not satisfy as *reliable*, the removal of the 10X safety factor imposed under FQPA is not defensible.

c) The actual finding of increased sensitivity of pups versus adults in the reproduction study confirms retention of the 10X safety factor imposed under FQPA for the protection of infants and children (note: I assert an opinion here that a clear consensus among external reviewers would have been expressed in support of this had they been aware that malathion has not been found in milk and that adult animals in the reproduction study were not affected at any dose level, while pup body weight gains were compromized at both the high dose and penultimate dose levels in this study. In further support of a finding that young individuals are more sensitive than older animals to malathion are three LD50 studies cited above showing greater sensitivity of

the young. The external toxicologists may not have known of these additional studies). Again, in view of the actual findings of enhanced sensitivity of the young, the removal of the 10X safety factor imposed under FQPA would be illegitimate.

d) Given the evidence of a post 3 months recovery of erythrocyte cholinesterase inhibition in females on lowering the food concentration from 100 to 50 ppm in the combined chronic toxicity/carcinogenicity study in the rat, 50 ppm cannot be concluded to have been a NOEL for the first three months of testing, particularly in view of the shallow dose response curve, where inhibition of the enzyme was 25%, 30%, 58% and 66% at the respective concentrations of 100, 500, 6000 and 12000 ppm via the diet. In other words, on the scale of dosing, there is too little difference between 50 and 100 ppm to readily accept that 50 ppm would have been a NOEL at the 3-months time point. In view of this, there is no NOEL for cholinesterase inhibition for females in this study, and hence, in the absence of any additional uncertainty factor, it cannot serve as the basis for the RfD.

e) Cholinesterase methodology may be a problem in this study which needs to be addressed.

f) A shift from the human study to the rat study as the basis for the RfD is unsupported.

g) Use of a mere 10X safety factor to allow for "uncertainties" (knowing of the lack of carboxylesterase in human plasma) in interspecies variability is held to be inadequate should the rat study supplant the human study.

h) Retinal tissue histopathology slides should be submitted for independent pathology assessment as called for in the study DER, and retinal tissues slides not taken from lower dose group animals should be submitted, according to Guideline requirements.

i) Additional behavioral effects testing, e.g. developmental neurotoxicity, should be required for malathion as is being done for certain other cholinesterase inhibiting pesticides.

j) Additional testing in animal models should be required to quantitate any gender specific disparity with respect to cholinesterase inhibition.

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